REMARKS

Reconsideration and allowance are respectfully requested.

Claims 8-12, 14, 18-20 and 23-31 are pending. The amendments are clearly supported by the original disclosure and, thus, no new matter is added by their entry. For example, claims 30-31 are supported by page 21, lines 10-11; page 23, lines 17-18; and page 24, line 20, of the specification.

The Examiner is respectfully requested to reconsider the restriction requirement as applied to non-elected claims 8, 14 and 20 because they share with elected claims 9 and 11 the special technical feature of administering a proline specific endoprotease for ingestion by a patient. Further, he is respectfully requested to reconsider the restriction of non-elected claims 18-19 from elected claim 8 because they share the special technical feature of digesting food with a proline specific endoprotease.

Specification Objections

The specification was objected to by the Examiner. The hyperlink is deleted since sources for the protease described by each EC number are well known in the art.

Withdrawal of the objection is requested.

35 U.S.C. 103 – Nonobviousness

A claimed invention is unpatentable if the differences between it and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art. *In re Kahn*, 78 USPQ2d 1329, 1334 (Fed. Cir. 2006) citing *Graham v. John Deere*, 148 USPQ 459 (1966). The *Graham* analysis needs to be made explicitly. *KSR v. Teleflex*, 82 USPQ2d 1385, 1396 (2007). It requires findings of fact and a rational basis for combining the prior art disclosures to produce the claimed invention. See id. ("Often, it will be necessary for a court to look to interrelated teachings of multiple patents . . . and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue"). The use of hindsight reasoning is impermissible. See id. at 1397

("A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon ex post reasoning"). Thus, a prima facie case under Section 103(a) requires "some rationale, articulation, or reasoned basis to explain why the conclusion of obviousness is correct." *Kahn* at 1335; see *KSR* at 1396. An inquiry is required as to "whether the improvement is more than the predictable use of prior art elements according to their established functions." Id. at 1396. But a claim that is directed to a combination of prior art elements "is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." Id. Finally, a determination of prima facie obviousness requires a reasonable expectation of success. See *In re Rinehart*, 189 USPQ 143, 148 (C.C.P.A. 1976).

Claims 9-12 were rejected under Section 103(a) as allegedly unpatentable over Messer et al. (Lancet 2:1022, 1976) in view of Hausch et al. (Am. J. Physiol. 283:G996-G1003, 2002) and Dekker et al. (WO 02/45524). Applicants traverse.

The Examiner admitted that Messer did not use a proline specific endoprotease as required by Applicants' claims. But that is not the only difference between the cited document and the present invention. Messer teaches enzyme therapy for celiac disease patients using papain in the form of enteric coated tablets. The third paragraph states, "All four enzymes are active at pH 7 and should therefore be able to act within the small intestine." At the bottom of the first column, it is mentioned that the crude papain is used in enteric-coated form. The enteric coating is used to protect the papain from gastric juices of the stomach. Only after passage through the stomach is the papain liberated from the coating and activated. Thus, Messer teaches using an enzyme that must be protected during passage through the stomach, which has conditions of low gastric pH, and that enzyme only becomes active at the neutral conditions found in the intestine. The present claims relate to enzyme therapy under acidic conditions of the stomach. Here, all of the elected claims recite a requirement for activity at acidic pH, mention explicitly this condition, or require an enzyme active at acidic pH or having an acidic pH optimum. By contrast, Messer teaches away from having the protease active in the stomach because the papain is protected from hydrolysis by an enteric coating.

Messer does not teach or suggest enzyme therapy where the protease is active in the stomach. Instead the protease is protected from gastric pH by an enteric coating until the protease passes to the neutral intestine. The advantage of using Applicants' proline specific endoprotease, which is active in the stomach rather than in the intestine, is that most, if not all, of the gliadin peptides are already broken down before entering the intestine. These peptides are of utmost importance because recognition of the toxic gluten epitopes takes place immediately downstream of the stomach. The residence time of food in the stomach is in general between 30 and 120 minutes, so the proline specific endoprotease has enough time to do its work in the stomach before toxic recognition of the gluten epitopes occurs. Hydrolysis of proline rich peptides by proline specific endoprotease before their entry into the intestine has the advantage that the peptides do not have the opportunity to have a harmful effect in the intestine, whereas Messer does not prevent their entry because the papain only becomes active after the peptides have entered the intestine. The beginning of the intestine is an especially harmful location acted on by the undigested gliadin peptides. The prior art fails to teach or suggest this advantage of Applicants' administering proline specific endoprotease for ingestion by the patient such that the protease is active under the acidic conditions of the patient's stomach. Thus, the difference in locations (stomach vs. intestine) provides an unexpected result obtained by practicing Applicants' claimed invention.

The Examiner alleged that Hausch disclosed immunodominant gliadin peptides that are related to the cause of celiac disease or gluten intolerance, and showed that these proline and glutamine rich peptides are exceptionally resistant to enzymatic digestion in patients with such disorders as celiac disease (see the Abstract and Discussion). Hausch arrived at this conclusion from the results of using soluble proteases from bovine and porcine pancreas, or brush-border membrane (BBM) from rat intestine. A similar conclusion was drawn from analogous studies with BBM from a human intestinal biopsy. Specifically, the cited document supplemented bacterial prolyl endopeptidase (PEP) with rat BBM to rapidly destroy immunodominant epitopes of these peptides. Hausch suggested a possible enzyme therapy strategy for celiac sprue (see Abstract's ending), "Supplementation of the BBM with trace quantities of a bacterial prolyl endo-

peptidase (PEP) leads to rapid cleavage of these gliadin peptides to units much smaller than the binding site of the HLA molecules" (page G997). Thus, Hausch teaches that bacterial PEP activity should be added as a supplement to BBM, which is only found in the intestine. Hausch's Figure 4 showed digestion of an enzyme-resistant peptide by endogenous proteases of BBM supplemented with exogenous PEP. Further, human intestinal BBM-mediated digestion of immunodominant gliadin epitopes was shown in Hausch's Figure 3. The cited document concluded that rat BBM studies are also applicable to human intestinal digestion (see page G1000). The present claims relate to enzyme therapy under acidic conditions of the stomach. Here, all of the elected claims recite a requirement for activity at acidic pH, mention explicitly this condition, or require an enzyme active at acidic pH or having an acidic pH optimum. By contrast, Hausch teaches away from having the protease active in the stomach because the cited document's suggested enzyme therapy relies on BBM-mediated proteolytic digestion in the intestine.

Hausch does not teach or suggest enzyme therapy where the protease is active in the stomach. Instead the endogenous protease activity is derived from BBM and it is supplemented with exogenous PEP active in the intestine. Contradicting the suggestion of the cited document, Applicants' claimed invention is focused on exogenous PEP activity under the acidic conditions of the stomach. This difference is critical because the pH conditions in the intestine and stomach are completely different. Whereas the stomach has acidic surrounding, less than pH 6 but usually between pH 2 and 5, the intestine has neutral to slightly alkaline conditions (pH between 7 and 8). The acidic chyme from the stomach is quickly neutralized early in the intestinal tract through the release of an alkaline solution by the pancreas, bringing the pH back up to around 7. As noted above, hydrolysis of proline rich peptides by proline specific endoprotease before their entry into the intestine has the advantage that the peptides do not have the opportunity to have a harmful effect in the intestine, whereas Hausch does not prevent their entry because the peptide would be digested after passage through the stomach. Hausch's protease is *Flavobacterium meningosepticum* PEP, which have a pH optimum between pH 7 and 8. Thus, it is well suited for use in the intestine but not in the stomach. The pH

optima of PEP from *Flavobacterium meningosepticum* and the PEP used in Applicants' examples are shown in Figure 3 of the present specification. *Flavobacterium meningosepticum* PEP has no or hardly any activity at pH of 5 and lower (i.e., acidic conditions of the stomach). The prior art fails to teach or suggest this advantage of Applicants' administering proline specific endoprotease for ingestion by the patient such that the protease is active under the acidic conditions of the patient's stomach. Thus, the difference in locations (stomach vs. intestine) provides an unexpected result obtained by practicing Applicants' claimed invention.

Messer and Hausch fail to render obvious Applicants' claimed invention because they teach enzyme therapy where the protease is active in the intestine. This failure is not remedied by combining their disclosures with Dekker, which discloses the use of a proline specific endoprotease in the context of *in vitro* digestion only (e.g., preparation of food outside the body prior to ingestion), because their combined disclosures would merely make obvious enzyme therapy in the intestine. Messer's and Hausch's disclosures actually teach away from targeting a protease to the stomach for enzyme activity because they relate to the advantage of activating protease activity farther downstream in the digestive tract. Further, there is no evidence presented in the Office Action of a reasonable expectation of success to use proline specific endoprotease that is active in the patient's stomach for treatment of celiac disease. Messer and Hausch are limited to enzyme therapy in the intestine; Dekker neither teaches nor suggests enzyme therapy for treatment of a celiac disease patient. Therefore, Applicants' claims are patentable over Messer in view of Hausch and Dekker.

Withdrawal of the Section 103 rejection is requested because the claims would not have been obvious to one of ordinary skill in the art when this invention was made.

Conclusion

Having fully responded to the pending Office Action, Applicants submit that the claims are in condition for allowance and earnestly solicit an early Notice to that effect. The Examiner is invited to contact the undersigned if additional information is required.

Respectfully submitted,

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